Applicants reserve the right to refile claims to the non-elected invention in one or more future applications retaining the priority date of the present case and the earlier cited priority applications.

III. Status of the Claims

Claim 4, representing the Group II invention, has been cancelled without prejudice and without disclaimer as being drawn to a non-elected invention. Claim 2 has been cancelled without prejudice and without disclaimer. Claim 1 has been amended. New claims 5-7 have been added.

Claims 1, 3, and 5-7 are therefore presently pending in the case. For the convenience of the Examiner, a clean copy of the pending claims is attached hereto as **Exhibit A**. In compliance with 37 C.F.R. § 1.121(c)(1)(ii), a marked up copy of the original claims is attached hereto as **Exhibit B**.

IV. Support for the Amended and Newly Added Claims

Claim 1 has been amended to further clarify the claim, and to recite that the isolated nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:1. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least in claim 1 as originally filed and in Section 5.1.

Claims 5 and 6 have been added to specifically recite recombinant expression vectors comprising isolated nucleic acid molecules of the invention. Support for these claims can be found throughout the specification as originally filed, with particular support being found at least at page 12, lines 14-21.

Claim 7 has been added to specifically recite host cells comprising the recombinant expression vectors of claim 5. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least at page 12, lines 21-27.

It will be understood that no new matter is included within the amended or newly added claims.

V. Rejection of Claims 1-3 Under 35 U.S.C. § 101

The Action first rejects claims 1-3 under 35 U.S.C. § 101, as allegedly lacking a patentable utility. Applicants respectfully traverse.

First, while Applicants in no way agree with the Examiner's position that claim 2 lacks a patentable utility, as claim 2 has been cancelled entirely without prejudice and without disclaimer solely in order to more rapidly progress the present case to allowance, the present rejection of claim 2 under

35 U.S.C. § 101 is rendered moot. The remainder of this section will therefore focus on claims 1 and 3.

As just one example of the utility of the present nucleotide sequences, the specification details on page 5, lines 2-4, that the present nucleotide sequences have utility in assessing gene expression patterns using high-throughput DNA chips. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. As the present sequences are specific markers of the human genome (see below), and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such DNA chips. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful.

Evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, two such companies (Agilent acquired by American Home Products and Rosetta acquired by Merck) were viewed to have such "real world" value that they were acquired by large pharmaceutical companies for significant sums of money. The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of

human genomic information has been clearly understood for many years).

Additionally, Applicants would like to invite the Examiner's attention to the fact that a sequence sharing nearly 100% percent identity at the protein level over an extended region of the claimed sequence is present in the leading scientific repository for biological sequence data (GenBank), and has been annotated by third party scientists who are *wholly unaffiliated with Applicants* as a "ADAMTSL3" (GenBank accession number AF237652; GenBank report shown in **Exhibit C**, alignment shown in **Exhibit D**). The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. Given this GenBank annotation, there can be no question that those skilled in the art would clearly believe that Applicants' sequence is an ADAMTS protease (the full length ADAMTSL3 sequence), as described in the specification as originally filed, at least at page 1, line 27 and page 14, line 28. Given the well established biological relevance of ADAMTS proteins, those of skill in the art would readily appreciate the utility of the present sequence in numerous applications, such as in the DNA chip applications described above.

Although Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as a further example of the utility of the presently claimed polynucleotide, as described in the specification at least at page 9, line 37, the present nucleotide sequence has a specific utility in determining the genomic structure of the corresponding human chromosome, for example mapping the protein encoding regions. This is evidenced by the fact that SEQ ID NO:1 can be used to map the 29 coding exons on chromosome 15 (present within four overlapping chromosome 15 clones; Genbank Accession Numbers AC027807, AC022684, AC116157 and AC087738; **Exhibit E**). Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of human chromosome 15 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic

acid sequence.

Only a minor percentage (2-4%) of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence, as described above. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). Applicants respectfully submit that the practical scientific value of biologically validated, expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence in support of the Applicants' position, the Examiner is requested to review, for example, section 3 of Venter *et al.* (*supra at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Rather, as set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable (*State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

The Action states that the present sequence lacks utility because "any diseases or conditions caused or exacerbated by the nucleic acid of SEQ ID NO:1" are not provided (Action bridging pages 3 and 4). However, this is not the standard required for utility under 35 U.S.C. § 101. In *In re Brana*, (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O.

for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. The Action goes on to state that the claimed sequences lack utility because "further research" (Action at page 4) would be required in certain aspects of the invention. Even if, *arguendo*, further research might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana*, which clearly states, as highlighted in the quote above, that "pharmaceutical inventions, necessarily includes the expectation of further research and development" (*Brana* at 1442-1443, emphasis added). In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8

USPQ 2d 1400 (Fed. Cir. 1988).

Finally, the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the Patent and Trademark Office ("the PTO") itself for compliance with 35 U.S.C. § 101. While Applicants are well aware of the new Utility Guidelines set forth by the USPTO, Applicants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Applicants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotides), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section VI, below), Applicants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Applicants understand that each application is examined on its own merits, Applicants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Applicants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, Applicants submit that as the presently claimed nucleic acid molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of claims 1-3 under 35 U.S.C. § 101 has been overcome, and request that the rejection be withdrawn.

VI. Rejection of Claims 1-3 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1-3 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

First, while Applicants in no way agree with the Examiner's position that one skilled in the art would not know how to use the invention as set forth in claim 2, since claim 2 has been cancelled entirely without prejudice and without disclaimer solely in order to more rapidly progress the present case to allowance, the present rejection of claim 2 under 35 U.S.C. § 112, first paragraph is rendered moot. The remainder of this section will therefore focus on claims 1 and 3.

Applicants submit that as claims 1 and 3 have been shown to have "a specific, substantial, and credible utility", as detailed in section V above, the present rejection of claims 1 and 3 under 35 U.S.C. § 112, first paragraph, cannot stand.

Applicants therefore request that the rejection of claims 1-3 under 35 U.S.C. § 112, first paragraph, be withdrawn.

VII. Rejection of Claim 2 Under 35 U.S.C. § 112, Second Paragraph

The Action next rejects claim 2 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the invention.

The Action rejects claim 2 as allegedly indefinite based on the term "stringent hybridization conditions". While Applicants submit that the term is sufficiently definite, as a number of stringent hybridization conditions are defined in the specification and would be known to those of skill in the art, as claim 2 has been cancelled without prejudice and without disclaimer solely in order to progress the case more rapidly toward allowance, the present rejection of claim 2 under 35 U.S.C. § 112, second paragraph has been rendered moot. Applicants therefore request withdrawal of this rejection.

VIII. Rejection of Claim 1 Under 35 U.S.C. § 102(a)

The Action next rejects claim 1 under 35 U.S.C. § 102(a), as allegedly anticipated by Mahairas *et al.* (Proc. Natl. Acad. Sci. USA 96:9739-9744, 1999 and Genbank Accession No. AQ743958; "Mahairas"). While Applicants do not necessarily agree with the present rejection, as claim 1 has been amended to recite the complete nucleotide sequence of SEQ ID NO:1, which is neither taught nor

suggested by Hillier. Applicants submit that the rejection of claim 1 under 35 U.S.C. § 102(a) has been overcome, and respectfully request withdrawal of the rejection.

IX. Rejection of Claim 1 Under 35 U.S.C. § 102(b)

The Action next rejects claim 1 under 35 U.S.C. § 102(b), as allegedly anticipated by Bonaldo *et al.* (Genome Res. *6*:791-806, 1996 and Genbank Accession No. BF543337; "Bonaldo"). While Applicants do not necessarily agree with the present rejection, as claim 1 has been amended to recite the complete nucleotide sequence of SEQ ID NO:1, which is neither taught nor suggested by Bonaldo, Applicants submit that the rejection of claim 1 under 35 U.S.C. § 102(b) has been overcome, and respectfully request withdrawal of the rejection.

X. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Snedden have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

February 13, 2003
Date

David W. Hibler Reg. No. 41,071
Agent for Applicants

LEXICON GENETICS INCORPORATED
8800 Technology Forest Place
The Woodlands, TX 77381
(281) 863-3399

Exhibit A

Clean Version of The Pending Claims in U.S. Patent Application Ser. No. 09/784,358

1. (Amended) An isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1.

3. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:2.

5. (New) A recombinant expression vector comprising the isolated nucleic acid molecule of claim 3.

6. (New) The recombinant expression vector of claim 5, wherein the isolated nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:1.

7. (New) A host cell comprising the recombinant expression vector of claim 5.

Exhibit B

Marked Up Version of Amended Claims in U.S. Patent Application Ser. No. 09/784,358

1. (Amended) An isolated nucleic acid molecule comprising [at least 24 contiguous bases of] the nucleotide sequence [first disclosed in] of SEQ ID NO:1.

2. (Cancelled) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO:2; and

(b) hybridizes under stringent conditions to the nucleotide sequence of SEQ ID NO:1 or the complement thereof.

3. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:2.

4. (Cancelled) An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:16.

5. (New) A recombinant expression vector comprising the isolated nucleic acid molecule of claim 3.

6. (New) The recombinant expression vector of claim 5, wherein the isolated nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:1.

7. (New) A host cell comprising the recombinant expression vector of claim 5.